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*turoctocog alfa pegol*

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# MOVE BEYOND THE THRESHOLD


As an extended half-life recombinant FVIII, Esperoct® offers a simple way to reach higher trough FVIII activity levels compared to standard half-life treatments.**[1,4-10]

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In adults and adolescents† with severe haemophilia A, Esperoct® demonstrated:

**A simple, fixed starting dose:**[1,4]
50 IU/kg every 4 days

**Higher trough FVIII activity levels vs. SHL treatments:**[1,4-10]
Mean trough FVIII activity levels of 3%

**Low ABR:**[1,4]
Median total ABR‡ of 1.18

*40°C storage for up to 3 months before reconstitution[1] **Esperoct® is licenced for the treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency)[1]

This advertisement is intended for Healthcare Professionals

**Prescribing Information**

## Esperoct®▼

Esperoct 500 IU Esperoct 1000 IU Esperoct 1500 IU Esperoct 2000 IU Esperoct 3000 IU (powder and solvent for solution for injection) Turoctocog alfa pegol. Human factor VIII, produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line, and no additives of human or animal origin are used in the cell culture, purification, conjugation or formulation. **Indication:** Treatment and prophylaxis of bleeding in patients 12 years and above with haemophilia A (congenital factor VIII deficiency) **Posology and administration:** The dose, dosing interval and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding, on the targeted factor VIII activity level and the patient's clinical condition. On demand treatment and treatment of bleeding episodes: Required dose IU = body weight (kg) x desired factor VIII rise (%) (IU/dL) x 0.5 (IU/kg per IU/dL). *Mild haemorrhage*: early haemarthrosis, mild muscle bleeding or mild oral bleeding. Factor VIII level required (IU/dL or % of normal): 20-40. Frequency of doses: 12-24, until the bleeding is resolved. *Moderate haemorrhage:* More extensive haemarthrosis, muscle bleeding, haematoma. Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses: 12-24, until the bleeding is resolved. *Severe or life-threatening haemorrhages:* Factor VIII level required (IU/dL or % of normal) – 60-100. Frequency of doses: 8-24, until the threat is resolved. Perioperative management: *Minor surgery Including tooth extraction.* Factor VIII level required (IU/dL or % of normal): 30-60. Frequency of doses (hours): within one hour before surgery; repeat after 24 hours if necessary. Duration of therapy: single dose or repeat injection every 24 hours for at least 1 day until healing is achieved. *Major surgery.* Factor VIII level required (IU/dL or % of normal): 80-100 (pre- and post-operative). Frequency of doses (hours): Within one hour before surgery to achieve factor VIII activity within the target range. Repeat every 8 to 24 hours to maintain factor VIII activity within the target range. Repeat injection every 8 to 24 hours as necessary until adequate wound healing is achieved. Consider continuing therapy for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL). Prophylaxis: The recommended starting dose is 50 IU of Esperoct per kg body weight every 4 days. The maximum single dose is 75 IU/kg. Adjustments of doses and administration intervals may be considered based on achieved factor VIII levels and individual bleeding tendency. Paediatric population: The dose in adolescents (12 years and above) is the same as for adults. In children below 12 years long-term safety has not been established. Method of administration: Intravenous injection (over approximately 2 minutes) after reconstitution of the powder with 4 mL supplied solvent (sodium chloride 9 mg/mL (0.9%) solution for injection). **Contraindications:** Hypersensitivity to the active substance or to any of the excipients, or to hamster protein. **Special warnings and precautions for use**: Hypersensitivity: Allergic-type hypersensitivity reactions are possible due to traces of hamster proteins, which in some patients may cause allergic reactions. If symptoms of hypersensitivity occur, patients should be advised to immediately discontinue the use of the medicinal product and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. In case of shock, standard medical treatment for shock should be implemented. Inhibitors: The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon. The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors. Patients treated with coagulation factor VIII products should be monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Cardiovascular events: In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk. Catheter-related complications: If a central venous access device (CVAD) is required, the risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered. Paediatric population: Listed warnings and precautions apply both to adults and adolescents (12-18 years). Excipient-related considerations: Product contains 30.5 mg sodium per reconstituted vial, equivalent to 1.5% of the WHO recommended maximum daily intake of 2.0 g sodium for an adult. **Fertility, pregnancy and lactation:** Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated. **Undesirable effects**: The Summary of Product Characteristics (SmPC) should be consulted for a full list of side effects. Common (≥ 1/100 to < 1/10): Rash, erythema, pruritus, injection site reactions. Uncommon (≥1/1,000 to <1/100): Factor VIII inhibition, hypersensitivity. **MA numbers and Basic NHS Price:** Esperoct 500 IU EU/1/19/1374/001 £425 Esperoct 1000 IU EU/1/19/1374/002 £850 Esperoct 1500 IU EU/1/19/1374/003 £1,275 Esperoct 2000 IU EU/1/19/1374/004 £1,700 Esperoct 3000 IU EU/1/19/1374/005 £2,550 **Legal category:** POM. **For full prescribing information please refer to the SmPC** which can be obtained from: Novo Nordisk Limited, 3 City Place, Beehive Ring Road, Gatwick, West Sussex, RH6 0PA. **Marketing Authorisation Holder:** Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised:** March 2020

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†Previously treated patients, 12 years and above[1]

‡Total ABR includes all bleeds: spontaneous, traumatic and joint bleeds[4]

**References: 1.** Esperoct® Summary of Product Characteristics. **2.** Adynovi® Summary of Product Characteristics. **3.** Elocta® Summary of Product Characteristics. **4.** Giangrande P et al. Thromb Haemost 2017; 117:252–261. **5.** Tiede A et al. J Thromb Haemost 2013; 11:670–678. **6.** Advate® Summary of Product Characteristics. **7.** Kogenate® Summary of Product Characteristics. **8.** NovoEight® Summary of Product Characteristics. **9.** Nuwiq® Summary of Product Characteristics. **10.** Refacto AF® Summary of Product Characteristics.

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bjh research paper

# Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England

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## Summary

The study objectives were to examine the association of maternal haemoglobin with stillbirth and perinatal death in a multi-ethnic population in England. We conducted a retrospective cohort analysis using anonymised maternity data from 14 001 women with singleton pregnancies ≥24 weeks' gestation giving birth between 2013 and 2015 in two hospitals - the Royal Wolverhampton NHS Trust and Guy's and St Thomas' NHS Foundation Trust. Multivariable logistic regression analyses were undertaken to analyse the associations between maternal haemoglobin at first visit and at 28 weeks with stillbirth and perinatal death, adjusting for 11 other risk factors. Results showed that 46% of the study population had anaemia (haemoglobin <110 g/l) at some point during their pregnancy. The risk of stillbirth and perinatal death decreased linearly per unit increase in haemoglobin concentration at first visit (adjusted odds ratio [aOR] stillbirth = 0·70, 95% confidence interval [CI] 0·58–0·85, aOR perinatal death = 0·71, 95% CI 0·60–0·84) and at 28 weeks (aOR stillbirth = 0·83, 95% CI 0·66–1·04; aOR perinatal death = 0·86, 95%CI 0·67–1·12). Compared with women with haemoglobin ≥110 g/l, the risk of stillbirth and perinatal death was five- and three-fold higher in women with moderate-severe anaemia (haemoglobin <100 g/l) at first visit and 28 weeks, respectively. These findings have clinical and public health importance.

**Keywords:** haemoglobin concentration, pregnancy, stillbirth, perinatal death, maternal anaemia.

There is increasing acceptance that anaemia affects patient outcomes. Pre-operative anaemia has an adverse impact on surgical outcomes, and this has driven changes in patient care pathways to attempt optimisation of a patient's haemoglobin before surgery (Musallam *et al*, 2011). Anaemia is also highly prevalent in pregnancy, and is by far most commonly caused by iron deficiency. Arguably, a lack of clarity on the full clinical consequences of anaemia has contributed to the lack of a comprehensive systematic approach to address this public health issue during pregnancy. One recent study in the UK showed that 24% of women developed anaemia at some point during their pregnancy (Barroso *et al*, 2011). A systematic review of 48 randomised controlled trials and 44 cohort studies provided evidence about the benefits of routine iron supplementation for selected outcomes, including improving maternal haemoglobin concentration and child birth-weight, but there was considerable uncertainty about the magnitude of the effects on most other maternal and infant outcomes including stillbirth and perinatal death due to a lack of studies (Haider *et al*, 2013).


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It is thought that most stillbirths are preventable and the causes are considered to be inextricably linked with the health of the mother (Frøen *et al*, 2016). In the UK, 3252 babies were stillborn in 2014, giving an incidence of 4·16 per 1000 total births (Manktelow *et al*, 2016). The stillbirth rate in the UK appears high compared with other high income countries (Lawn *et al*, 2016). One potential aetiological factor in the cause of stillbirth is iron deficiency anaemia, however, there is discussion in the literature about the strength of data supporting any association between haemoglobin concentration and stillbirth or levels of evidence on the effects of iron supplementation (Lawn *et al*, 2011).

The objective of this study was to further examine the association of maternal haemoglobin concentration at first antenatal visit and at 28 weeks with stillbirth and perinatal death by using very recent maternity data from large multi-ethnic populations at two urban hospitals in England.

## Methods

We conducted a retrospective cohort analysis using anonymised maternity data from 14 001 women with singleton pregnancies ≥24 weeks of gestation giving birth in two hospitals between 2013 and 2015 (7175 from Royal Wolverhampton NHS Trust, 2013–2014 and 6826 from Guy's and St Thomas' NHS Foundation Trust, 2014–2015). We examined the association between maternal haemoglobin and both stillbirth and perinatal death. These two outcomes clearly overlap, perinatal death being a composite of stillbirths and neonatal deaths in the first 7 days of life. However, both are frequently used as outcome measures.

Information on infant outcomes, live-birth, stillbirth at or after $24^{+0}$ weeks' gestation, and neonatal death in the first week of life were used to generate the outcome variables 'stillbirth' and 'perinatal death'. Information on maternal haemoglobin concentration at first visit and at 28 weeks was extracted from the hospital pathology systems and then paired with the maternity data. The datasets were then anonymised. We tested this exposure variable for deviations from linearity by fitting functional polynomials in the univariable logistic regression models with multiple transformations of the continuous variable (Royston *et al*, 1999). Results did not show the presence of any significant non-linear associations between maternal haemoglobin and the outcomes. We therefore used maternal haemoglobin as a continuous variable for the analysis.

Other known risk factors for stillbirth and perinatal mortality are advanced maternal age (>35 years), low socioeconomic status, ethnicity, high body mass index (BMI), nulliparity, smoking, antepartum haemorrhage, gestational diabetes, maternal infection and pregnancy-induced hypertensive disorders during the index pregnancy, pre-existing diabetes mellitus, and other pre-existing medical co-morbidities (such as mental health problems, hypertension, haemoglobinopathies), placental dysfunction, fetal growth restriction and spontaneous preterm labour (Di Mario *et al*, 2007; Flenady *et al*, 2011; Lawn *et al*, 2016). Major confounders identified from the literature include hypertensive disorders of pregnancy, which are associated with a decreased plasma volume and therefore a relatively higher haemoglobin concentration, antepartum haemorrhage, which can lead to a fall in haemoglobin, low socioeconomic status, which could result in a low haemoglobin from poor nutrition, and other medical comorbidities, such as haemoglobinopathies (Di Mario *et al*, 2007; Flenady *et al*, 2011; Lawn *et al*, 2016).

Information on socio-demographic characteristics, obstetric history, current pregnancy problems, and medical co-morbidities were used to generate variables for potential confounders and other risk factors for stillbirth and perinatal death. Information on ethnicity was not available for about 16% of the study sample. In another study Knight *et al* (2009) included women with unknown ethnicity in the 'white' group because the re-distributed proportions matched more accurately with the estimated ethnic profiles in the UK population census (NHS England, 2006). The same was done in this study. Tests for deviations from linearity showed that maternal age had a linear association with the outcomes, but a non-linear association was observed for maternal BMI. Women were therefore divided into four standard groups: normal (18·5–24·9 kg/m$^2$), underweight (<18·5 kg/m$^2$), overweight (25-29·9 kg/m$^2$) and obese (≥30 kg/m$^2$). Parity was used as a continuous variable and women were divided into smokers and non-smokers based on their smoking status at booking.

Maternal records relating to problems during the index pregnancy were used to generate binary variables for antepartum haemorrhage, gestational diabetes and hypertensive disorders of pregnancy. Three binary variables were generated from the history of medical co-morbidities; pre-existing haemoglobinopathies, pre-existing diabetes mellitus and any other medical comorbidities (excluding obesity).

### *Statistical analysis*

We compared the characteristics of the study population with that of the general pregnant population in England using available data on maternal characteristics from the Hospital Episode Statistics (HES) database of the Health and Social Care Information Centre (HSCIC) [http://www.hscic.gov.uk/hes (Accessed 12 August 2015)]. We then undertook univariable analysis to examine the crude associations of the outcomes (stillbirth and perinatal death) with maternal haemoglobin concentration at first visit, usually in the first trimester, and at 28 weeks' gestation. Both these time points coincide with routine haematology measurements during pregnancy. Multivariable logistic regression models were built to analyse the association of maternal haemoglobin concentration with stillbirth and perinatal death separately for the first visit and at 28 weeks adjusting

for 11 other risk factors (maternal age, ethnicity, BMI, parity, smoking status, gestational diabetes, antepartum haemorrhage and hypertensive disorders of pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, and other medical comorbidities). We did not find any significant moderate to strong correlations among the independent variables. However haemoglobin concentrations at first visit and at 28 weeks were highly correlated (correlation coefficient 0·54, $P < 0·001$), hence we did not adjust for baseline haemoglobin status in the 28 weeks multivariable model. Studies have shown that maternal haemoglobin concentration is associated with fetal growth restriction and preterm birth, precursors for stillbirth and early neonatal mortality (Haider *et al*, 2013; Nair *et al*, 2016a). Therefore, fetal growth restriction and preterm birth were not included in the regression models.

Additional logistic regression analyses were conducted by dividing the women into categories of anaemia according to their haemoglobin concentration using the cut-offs suggested by the World Health Organisation (WHO) (no anaemia ≥110 g/l (reference group), mild anaemia 100–109 g/l; moderate-severe anaemia <100 g/l) (WHO 2011). The multivariable models for anaemia at first visit and at 28 weeks adjusted for the 11 other risk factors. The categorical variables for maternal anaemia at first visit and at 28 weeks were not highly correlated, hence the 28 weeks multivariable model also adjusted for baseline anaemia status.

We tested for plausible interactions between haemoglobin concentration and mother's ethnicity, and haemoglobin concentration and BMI by fitting interaction terms into each of the multivariable models followed by likelihood ratio testing (LR-test). No significant interactions were observed. Missing information was <2% for most variables, except BMI and smoking. Data were not assumed to be missing at random and a proxy variable was generated by categorising the missing data as a separate group for each variable. All analyses were performed using Stata version 13·1, SE (StataCorp, College Station, TX, USA).

### *Sensitivity analyses*

Data on index of multiple deprivation (IMD) quintiles, a measure of socioeconomic status, was available only in the Wolverhampton dataset, hence a sensitivity analysis was conducted using this data to measure the effect of IMD quintiles on the association between haemoglobin concentration and the outcomes by testing two models, one with IMD quintiles in addition to the other 11 variables and one without. The results did not vary with the inclusion and exclusion of IMD quintiles. Sensitivity analysis was conducted for variables with >1% missing information by redistributing the missing observations into the different categories of the variables; this did not materially change the results. A complete case analysis was also performed. Again the results did not differ from the original models.

### *Study power*

A logistic regression of the binary response variables, stillbirth and perinatal death, on a continuous variable of maternal haemoglobin concentration with a fixed sample size of 14 001 observations and 0·4% prevalence of stillbirth in the UK (Manktelow *et al*, 2016) had 80% power at a 0·05 significance level to detect an odds ratio (OR) of ≤0·69 or ≥1·46 per unit increase in haemoglobin concentration. For the anaemia analysis, the minimum sub-group sample of 279 with a prevalence range of 0·4% to 0·7% for the outcomes in the unexposed had 80% power to detect an OR of 3·30 or greater at a *P*-value of <0·05 (two-tailed), and the maximum sub-sample 2976 for the same range of prevalence had 80% power to detect an OR of 1·60 or greater at $P < 0·05$ (two-tailed).

## Results

Characteristics of the women with singleton pregnancies delivering at or after $24^{+0}$ weeks of gestation in relation to the study outcomes are shown in Table I. The median age of pregnant women in the study population was 30 years (range 14–53 years) and median BMI was 25 kg/m$^2$ (range 10–74 kg/m$^2$). More than a third of the pregnant women had a BMI ≥25 kg/m$^2$ (21% of the pregnant women were overweight and 17% were obese), 48% were multiparous, 13% smoked during pregnancy and 30% belonged to ethnic minority groups. Nearly a quarter of the women had one or more pre-existing medical problems and 18% had problems during the index pregnancy (0·4% antepartum haemorrhage, 5% gestational diabetes, 5% hypertensive disorders of pregnancy and approximately 7% had other problems).

In the study population, median haemoglobin concentration at first visit was 125 g/l (range 51·6– 191 g/l) and at 28 weeks it was 113 g/l (range 64–174 g/l). The prevalence of mild anaemia increased, from 5% at the first visit to 22% at 28 weeks, and the proportion of women with moderate-severe anaemia increased from 2% at first visit to 7% at 28 weeks. In 26% of the women who had a normal haemoglobin at first visit, the concentrations decreased to <110 g/l at 28 weeks and 23% of the women who had mild anaemia at first visit became moderate to severely anaemic at 28 weeks. For 18% of the women with anaemia at first visit, the haemoglobin concentrations improved to normal pregnancy concentrations at 28 weeks. Overall, 46% of the women were identified to have developed anaemia at some point during their pregnancy.

In total, 0·5% of singleton babies were stillborn (14 before 28 weeks of gestation and 62 after 28 completed weeks of gestation) and a further 34 (20 of which were born before 28 weeks) died during the first seven days after birth, leading to an overall 0·8% perinatal mortality rate in the study population. The proportions of stillbirths and perinatal deaths did not vary across the categories of age, parity, smoking

**Table I.** Characteristics of the study population in relation to the outcomes.

| Maternal characteristics ($N$ = 14 001) | Women with live born babies (%) $n$ = 13 925 | Women with stillborn babies (%) $n$ = 76 | Women with infants who were alive at seven completed days after birth (%) $n$ = 13 891 | Women whose babies were stillborn or died at <7 days after birth (%) $n$ = 110 |
|---|---|---|---|---|
| Age (years) | | | | |
| <20 | 535 (3·8) | 5 (6·6) | 530 (3·8) | 10 (9·1) |
| 20–24 | 2,240 (16·1) | 14 (18·4) | 2,235 (16·1) | 19 (17·3) |
| 25–29 | 3,656 (26·3) | 14 (18·4) | 3,649 (26·3) | 21 (19·1) |
| 30–34 | 4,152 (29·8) | 25 (32·9) | 4,141 (29·8) | 36 (32·7) |
| 35–39 | 2,453 (17·6) | 15 (19·7) | 2,449 (17·6) | 19 (17·3) |
| 40–44 | 644 (4·6) | 3 (4·0) | 642 (4·6) | 5 (4·5) |
| ≥45 | 52 (0·4) | 0 (0) | 52 (0·4) | 0 (0) |
| Missing | 193 (1·4) | 0 (0) | 193 (1·4) | 0 (0) |
| Parity | | | | |
| Nulliparous | 7,231 (51·9) | 36 (47·4) | 7,211 (51·9) | 56 (50·9) |
| Multiparous | 6,693 (48·1) | 40 (52·6) | 6,679 (48·1) | 54 (49·1) |
| Missing | 1 (0·01) | 0 (0) | 1 (0·01) | 0 (0) |
| Body mass index categories (kg/m$^2$)*,† | | | | |
| Underweight (<18·5) | 361 (2·6) | 1 (1·3) | 360 (2·6) | 2 (1·8) |
| Normal (18·5–24·9) | 4,801 (34·5) | 23 (30·3) | 4,788 (34·5) | 36 (32·7) |
| Overweight (25–29·9) | 2,978 (21·4) | 17 (22·4) | 2,970 (21·4) | 25 (22·7) |
| Obese (≥30) | 2,333 (16·7) | 23 (30·3) | 2,325 (16·7) | 31 (28·2) |
| Missing | 3,452 (24·8) | 12 (15·8) | 3,448 (24·8) | 16 (14·6) |
| Smoking status | | | | |
| Smoker | 1,808 (13·0) | 11 (14·5) | 1,803 (13·0) | 16 (14·5) |
| Non-smoker | 10,430 (74·9) | 60 (78·9) | 10,404 (74·9) | 86 (78·2) |
| Missing | 1,687 (12·1) | 5 (6·6) | 1,684 (12·1) | 8 (7·3) |
| Ethnicity | | | | |
| White | 9,722 (69·8) | 47 (61·8) | 9,698 (69·8) | 71 (64·6) |
| Non-white | 4,203 (30·2) | 29 (38·2) | 4,193 (30·2) | 39 (35·4) |
| Problems in current pregnancy | | | | |
| Antepartum haemorrhage† | | | | |
| No | 13,825 (99·3) | 74 (97·4) | 13,792 (99·3) | 107 (97·3) |
| Yes | 53 (0·4) | 1 (1·3) | 53 (0·4) | 1 (0·9) |
| Missing | 47 (0·3) | 1 (1·3) | 46 (0·3) | 2 (1·8) |
| Gestational diabetes mellitus† | | | | |
| No | 13,167 (94·6) | 69 (90·8) | 13,135 (94·6) | 101 (91·8) |
| Yes | 711 (5·1) | 6 (7·9) | 710 (5·1) | 7 (6·4) |
| Missing | 47 (0·3) | 1 (1·3) | 46 (0·3) | 2 (1·8) |
| Hypertensive disorders of pregnancy† | | | | |
| No | 13,177 (94·6) | 69 (90·8) | 13,147 (94·6) | 99 (90·0) |
| Yes | 694 (5·0) | 6 (7·9) | 691 (5·0) | 9 (8·2) |
| Missing | 54 (0·4) | 1 (1·3) | 53 (0·4) | 2 (1·8) |
| Pre-existing medical problems | | | | |
| Diabetes mellitus*,† | | | | |
| No | 13,693 (98·3) | 73 (96·1) | 13,661 (98·3) | 105 (95·5) |
| Yes | 219 (1·6) | 2 (2·6) | 217 (1·6) | 4 (3·6) |
| Missing | 13 (0·1) | 1 (1·3) | 13 (0·1) | 1 (0·9) |
| Haemoglobinopathies*,† | | | | |
| No | 13,832 (99·3) | 75 (98·7) | 13,798 (99·3) | 109 (99·1) |
| Yes | 80 (0·6) | 0 (0) | 80 (0·6) | 0 (0) |
| Missing | 13 (0·1) | 1 (1·3) | 13 (0·1) | 1 (0·9) |
| Others (except obesity)*,† | | | | |
| No | 11,033 (79·2) | 52 (68·4) | 11,009 (79·2) | 76 (69·1) |
| Yes | 2,879 (20·7) | 23 (30·3) | 2,869 (20·7) | 33 (30·0) |
| Missing | 13 (0·1) | 1 (1·3) | 13 (0·1) | 1 (0·9) |

*$P$ < 0·05 for chi square test for difference in proportion of stillbirths across the sub-groups.
†$P$ < 0·05 for chi square test for difference in proportion of perinatal deaths across the sub-groups.

status and ethnicity, but a higher proportion of stillbirth and perinatal death were observed among obese women and women with pre-existing medical comorbidities (Table I).

A comparison of the study population with that of the general population of pregnant women in England using routine national data showed that the age distribution, and proportions of multiparous women in the study population were comparable with that of the general pregnant population in England. However, the study population had a higher proportion of women from ethnic minority groups, particularly Indian, black Caribbean and black African (Table S1).

### *Maternal haemoglobin concentration and stillbirth*

The associations between maternal haemoglobin concentration and stillbirth are shown in Table II. In singleton babies born at or after $24^{+0}$ weeks of gestation, the crude odds of stillbirth decreased by 25% per unit increase in the haemoglobin concentration at first visit [OR = 0·75, 95% confidence interval (CI) 0·62–0·92, $P = 0·004$]. After adjusting for 11 other risk factors, the odds of stillbirth decreased by 30% per unit increase in the haemoglobin concentration (i.e. per 10 g/l increase in haemoglobin concentration) [adjusted odds ratio (aOR) = 0·70, 95% CI 0·58–0·85, $P = 0·001$]. The association between maternal haemoglobin concentration at 28 weeks and stillbirth was not statistically significant at $P < 0·05$, but an inverse linear association was observed (OR = 0·86, 95% CI 0·65–1·14, $P = 0·277$); aOR = 0·83, 95% CI 0·63–1·11, $P = 0·207$).

### *Maternal haemoglobin concentration and perinatal death*

As shown in Table II, the association between maternal haemoglobin concentration and perinatal death was comparable with the association between haemoglobin concentration and stillbirth. In singleton babies born at or after $24^{+0}$ weeks of gestation, the crude odds of perinatal death decreased by 25% per unit increase in the haemoglobin concentration at first visit (OR = 0·75, 95% CI 0·64–0·88, $P = 0·001$). After adjusting for the 11 risk factors, the odds of perinatal death decreased by 29% per unit increase in the haemoglobin concentration (aOR = 0·71, 95% CI 0·60–0·84, $P < 0·001$). The adjusted odds of perinatal death decreased by 13% per unit increase in haemoglobin concentration at 28 weeks, but the association was not statistically significant at $P < 0·05$ (OR = 0·87, 95% CI 0·68–1·13, $P = 0·290$; aOR = 0·86, 95% CI 0·67–1·12, $P = 0·272$).

### *Maternal anaemia and infant outcomes*

An examination of the association between maternal anaemia and the adverse outcomes further substantiated the results of the inverse association between haemoglobin concentration and the outcomes at both the first and 28 week visits. The odds of stillbirth and perinatal death were five-fold higher among pregnant women with moderate-severe anaemia compared with women who had no anaemia at first visit (Table III) after adjusting for the 11 other risk factors (aOR stillbirth = 4·97, 95% CI 2·09–11·79, $P < 0·001$; aOR perinatal death = 5·16, 95% CI 2·53–10·52, $P < 0·001$). The odds of stillbirth and perinatal death were more than two and a half times higher among pregnant women with moderate-severe anaemia at 28 weeks of gestation after adjusting for the baseline anaemia status and 11 other risk factors compared with women with normal haemoglobin concentration at 28 weeks (aOR stillbirth = 2·81, 95% CI 1·25–6·30, $P = 0·012$; aOR perinatal death = 2·60, 95% CI 1·23–5·51, $P = 0·012$). The crude and adjusted odds ratios for stillbirth and perinatal death among women with mild anaemia were not significantly different compared to women who had no anaemia at first visit (aOR stillbirth = 0·56, 95% CI 0·13–2·30, $P = 0·416$; aOR perinatal death = 0·58, 95% CI 0·18–1·85, $P = 0·354$) or at 28 weeks (aOR stillbirth = 1·30, 95% CI 0·64–2·61, $P = 0·457$; aOR perinatal death = 1·27, 95% CI 0·68–2·38, $P = 0·446$).

## Discussion

This study confirms that the burden of anaemia is high: nearly half of the women (46%) in the study population had

**Table II.** Association of maternal haemoglobin concentration with adverse fetal and infant outcomes.

| Exposure | Stillbirth | Perinatal death |
|---|---|---|
| Maternal haemoglobin at first visit (g/l) | | |
| Unadjusted odds ratio (95% CI) per unit increase in haemoglobin concentration | 0·75 (0·62–0·92) | 0·75 (0·64–0·88) |
| Adjusted odds ratio† (95% CI) per unit increase in haemoglobin concentration | 0·70 (0·58–0·85) | 0·71 (0·60–0·84) |
| Maternal haemoglobin at 28 weeks (g/l)* | | |
| Unadjusted odds ratio (95% CI) per unit increase in haemoglobin concentration | 0·86 (0·65–1·14) | 0·83 (0·66–1·04) |
| Adjusted odds ratio† (95% CI) per unit increase in haemoglobin concentration | 0·83 (0·63–1·11) | 0·86 (0·67–1·12) |

$N = 14001$ singleton babies born at or after 24 weeks of gestation.

*The model at 28 weeks excludes women who had a stillbirth or perinatal death before 28 weeks.

†Model adjusted for maternal age, body mass index, parity, smoking status, gestational diabetes, antepartum haemorrhage and pregnancy-induced hypertension during index pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, other medical comorbidities and ethnicity; CI, Confidence Interval.

**Table III.** Association of maternal anaemia with adverse infant outcomes.

| | Stillbirth ($n$ = 14001 singleton babies born at or after $24^{+0}$ of gestation) | | | | | |
|---|---|---|---|---|---|---|
| Maternal anaemia | Stillborn (%) | Live born (%) | Unadjusted OR (95% CI) | *P*-value for trend | †Adjusted OR (95% CI) | *P*-value for trend |
| First visit (Hb, g/l) | | | | | | |
| Normal Hb (≥110) | 59 (77·6) | 11 529 (82·8) | 1 (ref) | 0·025 | 1 (ref) | 0·018 |
| Mild (100–109) | 2 (2·6) | 767 (5·5) | 0·51 (0·12–2·09) | | 0·56 (0·13–2·30) | |
| Moderate-severe (<100) | 6 (7·9) | 273 (2·0) | 4·29 (1·84–10·03) | | 4·97 (2·09–11·79) | |
| Missing | 9 (11·8) | 1356 (9·7) | 1·29 (0·64–2·62) | | 1·50 (0·73–3·11) | |
| 28 weeks (Hb, g/l)* | | | | | | |
| Normal Hb (≥110) | 26 (41·9) | 7833 (56·6) | 1 (ref) | 0·008 | 1 (ref) | 0·059 |
| Mild (100–109) | 12 (19·4) | 3007 (21·7) | 1·20 (0·61–2·39) | | 1·30 (0·64–2·61) | |
| Moderate-severe (<100) | 10 (16·1) | 988 (7·1) | 3·05 (1·47–6·34) | | 2·81 (1·25–6·30) | |
| Missing | 14 (22·6) | 2014 (14·6) | 2·09 (1·09–4·02) | | 1·84 (0·91–3·74) | |
| | Perinatal death ($n$ = 14001 singleton babies born at or after $24^{+0}$ weeks) | | | | | |
| Maternal anaemia | Perinatal death (%) | Alive at 7 completed days after birth (%) | Unadjusted OR (95% CI) | *P*-value for trend | †Adjusted OR (95% CI) | *P*-value for trend |
| First visit (Hb, g/l) | | | | | | |
| Normal Hb (≥110) | 83 (75·5) | 11,505 (82·8) | 1 (ref) | 0·003 | 1 (ref) | 0·003 |
| Mild (100–109) | 3 (2·7) | 766 (5·5) | 0·54 (0·17–1·72) | | 0·58 (0·18–1·85) | |
| Moderate-severe (<100) | 9 (8·2) | 270 (1·9) | 4·62 (2·29–9·28) | | 5·16 (2·53–10·52) | |
| Missing | 15 (13·6) | 1,350 (9·7) | 1·54 (0·88–2·67) | | 1·85 (1·05–3·26) | |
| 28 weeks (Hb, g/l)* | | | | | | |
| Normal Hb (≥110) | 32 (42·1) | 7,827 (56·6) | 1 (ref) | 0·013 | 1 (ref) | 0·059 |
| Mild (100–109) | 15 (19·7) | 3,004 (21·7) | 1·17 (0·67–2·05) | | 1·27 (0·68–2·38) | |
| Moderate-severe (<100) | 11 (14·5) | 987 (7·1) | 2·57 (1·37–4·82) | | 2·60 (1·23–5·51) | |
| Missing | 18 (23·7) | 2,010 (14·5) | 3·75 (2·41–5·84) | | 1·99 (1·06–3·71) | |

Hb- Haemoglobin; CI, Confidence Interval.

*Excludes 14 women with stillbirth and 34 women with perinatal death before 28 weeks.

†Model for first visit adjusted for maternal age, body mass index, parity, smoking status, gestational diabetes, antepartum haemorrhage and pregnancy-induced hypertension during index pregnancy, pre-existing diabetes mellitus, haemoglobinopathies, other medical comorbidities and ethnicity; Model for 28 weeks is adjusted for baseline anaemia status in addition to the other variables included in the first visit model.

anaemia at some point during their pregnancy. The need for haematologists and obstetricians to optimise local care pathways for recognition and management of anaemia is further reinforced by our main study findings suggesting that the risk of stillbirth and perinatal death decreased linearly per unit increase in haemoglobin concentration at first visit and at 28 weeks after accounting for 11 other known risk factors. Compared with women with normal haemoglobin concentrations, the risk of stillbirth and perinatal death was five-fold and three-fold higher in women with moderate-severe maternal anaemia at first visit and 28 weeks, respectively.

The inverse linear association of stillbirth and perinatal death with maternal haemoglobin concentration at 28 weeks of gestation was not statistically significant, possibly due to a low study power, however, the higher risk of adverse outcomes was still present among pregnant women with moderate-severe anaemia (haemoglobin <100 g/l) at 28 weeks. Overall, we believe our findings are important in the broader haematology, obstetric and public health context as it suggests that, given anaemia is most commonly related to iron deficiency, iron supplementation during pregnancy could have an incremental benefit on reducing the risk of stillbirth and perinatal death for all women.

Iron deficiency anaemia during pregnancy has been explored as a risk factor for stillbirth although the evidence is limited and conflicting (Lawn *et al*, 2011). A few studies from low-to-middle income countries have shown an association of maternal anaemia with stillbirth and perinatal death (Lone *et al*, 2004; Watson-Jones *et al*, 2007; Nair *et al*, 2016a), but others from high-income countries have not reported a significant association (Stephansson *et al*, 2000; Little *et al*, 2005). However, a study from the USA that used National Maternal and Infant Health Survey data from deliveries in 1988 (Tomashek *et al*, 2006) found a significantly higher risk of stillbirth among non-black women who have moderate anaemia. A prospective study from China (Zhang *et al*, 2009) found that haemoglobin <90 g/l in the third trimester of pregnancy was associated with a reduced risk of stillbirth. The authors did not adjust for important pregnancy complications, such as hypertensive disorders of

pregnancy, which can result in reduced plasma volume (and thereby an increase in haemoglobin concentration). Hypertensive disorders of pregnancy are known risk factors for stillbirth with a well-recognised aetiology. These disorders, particularly the pre-eclampsia syndrome, are associated with a reduced maternal intravascular volume and, consequently, a relatively higher haemoglobin concentration compared to unaffected pregnancies. Not adjusting for these important groups of disorders results in the potential for confounding and bias.

A study among Swedish pregnant women found a U-shaped association between stillbirth and haemoglobin concentration at first visit or at 28 weeks (Stephansson *et al*, 2000). In contrast to our findings, the Swedish study did not show a significant association between anaemia and stillbirth. One possible reason for this difference could be because the Swedish study did not account for the effect of important risk factors for stillbirth, including gestational diabetes and medical comorbidities; instead the multivariable models adjusted for small-for-gestational age, which has been hypothesised to be in the pathway mediating the effect of haemoglobin concentration on stillbirth (Stephansson *et al*, 2000). Another study using data from St Mary's Maternity Information System database (London) did not find a significant association between perinatal mortality and haemoglobin concentration at first antenatal visit, but showed a risk associated with lowest and highest haemoglobin concentrations recorded at any point during the pregnancy after the first visit (Little *et al*, 2005). A limitation of this study, as acknowledged by the authors, was that information for haemoglobin concentration was missing for more than a third of the study population. In addition, the authors did not adjust for important potential confounders.

The present study addresses a gap in the UK to explore evidence on the association between haemoglobin concentration and adverse fetal and infant outcomes. In addition to the already known association of low haemoglobin during pregnancy and maternal anaemia with poor maternal outcomes in the UK (Nair *et al*, 2016b), this study identified a significant association with stillbirth and perinatal death. The study population appears comparable with that of the general pregnant population in England in terms of age distribution, multiparity and multiple pregnancies, suggesting generalisability, although the study sample had a higher proportion of women from ethnic minority groups. We did not have information on BMI, smoking status and pregnancy problems in national data, and were unable to comment on the comparability of these factors to the general population. We did not have information on whether women in the study population were taking multivitamin or iron supplementation and therefore could not account for this in the analysis. However, according to the recommended guidance, in the study hospitals all pregnant women who are diagnosed with anaemia at any point during pregnancy should be prescribed iron supplementation.

There are several limitations to recognise in our analysis. We have defined haemoglobin thresholds during pregnancy as commonly reported in textbooks, but it is unclear to what degree these thresholds are validated reference ranges during pregnancy, even allowing for the effects of changes in plasma volume. Inability to adjust for socioeconomic status in the main multivariable models was a limitation, but sensitivity analysis using the Wolverhampton data did not show any significant effect of socioeconomic status on the association we observed between haemoglobin concentration and the outcomes. Another limitation was missing information on haemoglobin concentration at first visit and at 28 weeks for about 9·7% and 15·6% of the women, respectively, which could have biased the study results. However, the results of sensitivity analyses by redistributing the missing observations into the different categories of the anaemia variable, and complete case analysis were not materially different from that of the original models. We did not have information about the causes of stillbirth in the study population and were therefore not able to examine the association between maternal haemoglobin and stillbirth stratified by causes of stillbirth (for example, congenital anomalies).

## Conclusion

This study provides clear evidence of an association of stillbirth and perinatal death with maternal haemoglobin concentration at first visit and at 28 weeks of pregnancy in a multi-ethnic population in England. The risk of these adverse outcomes was significantly higher among women who had moderate-severe anaemia during pregnancy, but more importantly, this risk decreased linearly per unit increase in maternal haemoglobin concentration. This finding is of clinical and public health importance, given that high rates of stillbirth are a major issue globally and a high burden of anaemia is a common finding during pregnancy.

Anaemia is most commonly caused by iron deficiency. Current approaches to the management of anaemia during pregnancy are described in national guidelines (Pavord *et al*, 2012), based on reactive treatment following case identification. It is of note that nearly half of women in our study population developed anaemia at some point during their pregnancy, which is higher than that reported several years earlier in an epidemiological study (Barroso *et al*, 2011), suggesting significant on-going challenges in delivering the current policies for case identification and treatment. Alternative strategies to better manage anaemia during pregnancy appear to be an attractive option to improve maternal and fetal outcomes, alongside attention to factors such as obesity and smoking cessation. Routine iron supplementation during pregnancy can maintain normal haemoglobin concentrations and prevent many cases of maternal anaemia. Further experimental studies are required to investigate the effect of iron supplementation during pregnancy on fetal outcomes, assessing appropriate dosing and factors such as adherence and tolerability.

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## Author contribution

MN contributed to the design of the study, carried out the data analysis, interpreted the data, and wrote the first draft of the manuscript. DC designed the study, facilitated the process of data extraction from the hospital records, contributed to the data analysis plan and interpretation of the results, and edited the manuscript. SR facilitated the process of data extraction from the hospital records, contributed to interpretation of the results and edited the manuscript. CNP contributed to interpretation of the results and edited the manuscript. SS designed the study, contributed to the data analysis plan and data interpretation, and edited the manuscript. MK designed the study, contributed to the data analysis plan, data interpretation, and edited the manuscript.

## Ethical approval

Ethics approval was not required since this was a secondary analysis of anonymous hospital data.

## Disclosure of interest

The authors declare that they have no competing interests.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Comparison of characteristics of women giving birth in the study hospitals with that of the general population of pregnant women in England

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